

Airflow Limitation and Dynamic Gas Trapping in a Bone Marrow Transplant Recipient

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Introduction

Pulmonary complications are frequent in those who undergo allogeneic bone marrow transplantation. One of the more common presentations is that of obliterative bronchiolitis, which occurs in those who develop graft versus host disease (GVHD), itself a frequent occurrence in allogeneic bone marrow transplantation. The following case is a typical presentation of this disorder and discusses obliterative bronchiolitis and other pulmonary complications of bone marrow transplantation of which the health care provider should be aware.

Case Report

A 22-year-old man with chronic myelogenous leukemia 12 months after allogeneic bone marrow transplant presented with 3 days of fever, chills, headaches, myalgias, arthralgias, abdominal pain, nonproductive cough, and dyspnea. He reported inconsistent adherence with his medications and discontinuation of all medications over the preceding 3 weeks. His prescribed medical regimen included cyclosporine (75 mg twice daily), prednisone (20 mg daily), intravenous gamma globulin (once monthly), and double-strength trimethoprim/sulfamethoxazole (3 times a week). He had a 5-pack-year smoking history.

On examination, he appeared cachectic. His temperature was 37.1°C, heart rate 135 beats/min, blood pressure 109/60 mm Hg, and respiratory rate 36 breaths/min. Skin examination showed patchy areas of erythematous and hypopigmented skin lesions, predominately on the upper ex-

trimities and trunk. The oropharynx appeared dry, with mild angular ulceration. Examination of the lymph nodes, thyroid, heart, abdomen, and extremities was unremarkable. The chest examination was notable for diffuse rhonchi and wheezing.

Laboratory examination revealed a white blood cell count of 16,500/ μ L, with 31% bands. Hemoglobin, platelet count, coagulation studies, chemistry panel, renal function, and urinalysis were within normal limits. Liver function tests demonstrated mild cholestasis. Arterial blood gas analysis on admission showed pH 7.51, P_{aCO_2} 27 mm Hg, P_{aO_2} 41 mm Hg, and oxygen saturation of 81% while breathing room air. The chest radiograph was within normal limits. A computed tomography (CT) angiogram of the chest was negative for pulmonary embolism. High-resolution CT of the chest (Fig. 1) showed mosaic attenuation pattern that suggested hyperinflation and air trapping. Blood and sputum cultures were negative. Bronchoalveolar lavage fluid was negative for bacteria, fungi, viruses, or *Pneumocystis carinii*.

Pulmonary function tests (Table 1) obtained at the time of presentation showed a forced expiratory volume in the first second (FEV_1) of 29% of predicted and a forced vital capacity (FVC) of 40% of predicted. The FEV_1/FVC ratio was 64%. Lung volumes measured by the nitrogen wash-out technique demonstrated a markedly decreased total lung capacity and functional residual capacity (FRC), each at 59% of predicted. Residual volume was within normal limits. These findings were consistent with a mixed obstructive/restrictive ventilatory defect and markedly abnormal diffusion capacity. Compared to his pulmonary function tests before the bone marrow transplant (see Table 1), there was a substantial increase in airflow limitation, with a pronounced decline in lung volumes and gas exchange.

Given the apparent disconnect between the clinical manifestations of airflow limitation and the physiologic data showing reduced lung volumes, pulmonary function tests were repeated using a different methodology. Both FEV_1 and FVC measurements (see Table 1) were similar. However, lung volumes were remarkably different. Total lung capacity was 87% of predicted and FRC was 128% of

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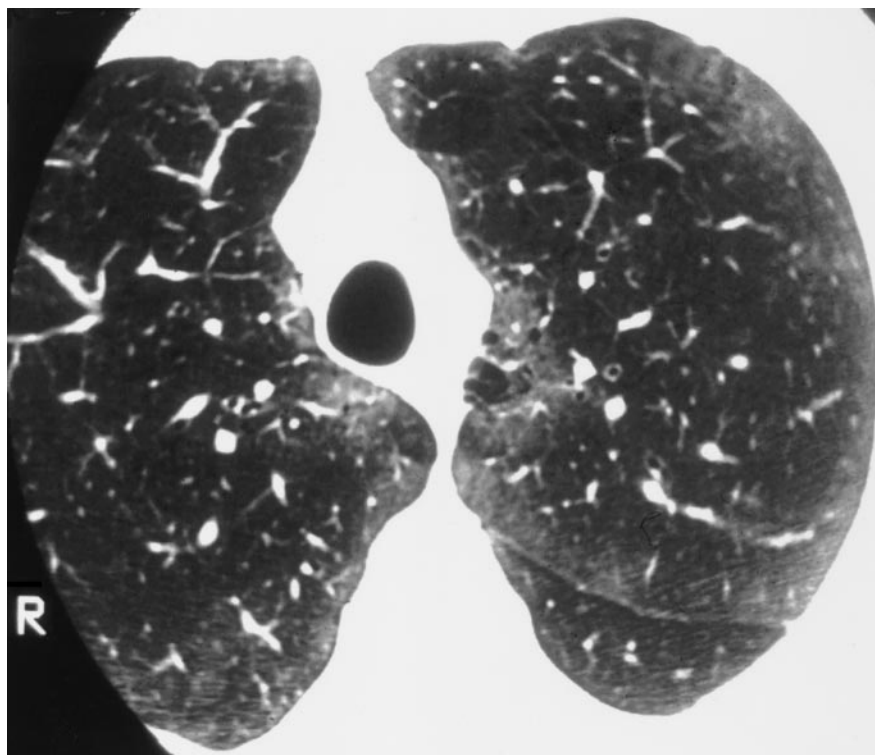


Fig. 1. High-resolution computed tomogram of the chest, obtained at full inspiration, showing patchy areas of decreased lung attenuation, with a reduction in the size of the blood vessels (mosaic perfusion).

predicted. Residual volume demonstrated marked air trapping, at 249% of predicted. Diffusion capacity measurements were not different.

The patient was treated with intravenous immunoglobulin and cyclosporine. High-dose corticosteroid therapy was initiated with methylprednisolone (125 mg intravenously, every 6 h). He slowly improved over the next few days, with resolution of his dyspnea and cough. His P_{aO_2} improved to 58 mm Hg two days after admission, and 2 weeks later at another hospital, situated at a lower altitude, his P_{aO_2} was 79 mm Hg.

The diagnosis was graft-versus-host disease (GVHD) complicated by obliterative bronchiolitis.

Discussion

Approximately 40–60% of allogeneic recipients develop multisystem GVHD, which can be associated with a myriad of pulmonary complications.^{1–5} Obliterative bronchiolitis occurs in approximately 10% of GVHD patients,⁵ with risk factors that include chronic GVHD, busulfan exposure, human leukocyte antigen mismatch, low post-bone-marrow-transplant immunoglobulin level, immunosuppression with methotrexate, and allogeneic as opposed to autologous bone marrow transplant.^{2–5} Most patients with post-bone-marrow-transplant obliterative bronchioli-

tis present with concomitant signs and symptoms of chronic GVHD. Typically, obliterative bronchiolitis presents 6–12 months after bone marrow transplant, with cough and dyspnea, but it has been described as early as 30 days and as late as 2 years after bone marrow transplant. However, more than 90% of patients who develop symptoms of obliterative bronchiolitis do so within the first 18 months after transplantation.⁵

Nonproductive cough and dyspnea are the major clinical manifestations of GVHD-associated obliterative bronchiolitis. Chest examination is often normal, but there may be evidence of hyperinflation and diminished breath sounds. Wheezing, inspiratory squeaks, or crackles may be present and are often seen early.⁵ Chest radiograph can be normal or show hyperinflation. High-resolution CT of the chest, with paired inspiratory and expiratory images, is the imaging study of choice, and the characteristic findings include variable attenuation of lung parenchyma due to air trapping (mosaic attenuation) and occasional airway dilatation. Physiologic testing typically shows moderate to severe airflow limitation, with hyperinflation and gas trapping. Restrictive or mixed defects may result from a concomitant interstitial process due to chemotherapy toxicity and/or lung irradiation.

Diagnosis of GVHD-associated obliterative bronchiolitis is based primarily on supportive clinical, laboratory,

Table 1. Pulmonary Function as Measured by Spirometry, Nitrogen Washout, and Body Plethysmography Techniques

	Predicted	Spirometry 4 Months Before BMT value and (% of predicted)	Nitrogen Washout value and (% of predicted)	Body Plethysmography value and (% of predicted)
FVC (L)	5.11	4.65 (80)	2.02 (40)	2.14 (37)
FEV ₁ (L)	4.45	4.31 (93)	1.29 (29)	1.09 (23)
FEV ₁ /FVC (%)	87	93	64	51
TLC (L)	6.91	NM	4.07 (59)	6.55 (87)
FRC (L)	4.30	NM	2.52 (59)	5.25 (128)
RV (L)	1.80	NM	1.95 (108)	4.49 (249)
SVC (L)	5.11	NM	2.12 (41)	NM
Washout time (min)	NA	NM	6.82	NA
Final N ₂ concentration (%)	NA	NA	2.58	NA
D _{LCO} (mL/min/mm Hg)	41.16	49.80 (121)	15.57 (38)	11.46 (33)
V _A (L)	7.09	NM	2.51 (35)	2.77 (36)
D _{LCO} /V _A (mL/min/mm Hg/L)	5.36	NM	6.21 (116)	4.14 (92)

BMT = bone marrow transplant

FVC = forced vital capacity

FEV₁ = forced expiratory volume in the first second

TLC = total lung capacity

NM = not measured

FRC = functional residual capacity

RV = residual volume

SVC = slow vital capacity

NA = not applicable

D_{LCO} = diffusing capacity of the lung for carbon monoxide

V_A = alveolar volume

and physiologic features. Definitive diagnosis typically requires open-lung biopsy, but, given the increased risks associated with surgical procedures in this patient population, it is believed that surgical biopsy can be avoided when a consistent clinical picture is present. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy may be performed to help exclude infectious causes. However, the sensitivity of transbronchial biopsy for diagnosing obliterative bronchiolitis is limited by the patchy small airways involvement characteristic of the disease.² Histopathology classically shows bronchiolar and peribronchiolar lymphocytic infiltrate with concentric fibrosis and partial to complete obliteration of affected bronchioles.⁵ Thus, a characteristic clinical picture with supporting physiologic, radiographic, and laboratory data is paramount for obtaining a timely diagnosis on which to initiate aggressive therapy.

Treatment of GVHD-associated obliterative bronchiolitis consists of reinstatement or augmentation of immunosuppression. Corticosteroids are the mainstay of treatment, at a dose of 1.0–1.5 mg/kg/d (maximum dose of 100 mg/d) for 2–6 weeks, followed by tapering of dose on clinical improvement or stabilization.⁵ Prognosis of GVHD-associated obliterative bronchiolitis is poor: overall 3-year mortality is 65%.⁴ Some patients may respond to initial therapy, but substantial improvement in lung function is rare. Despite improvement in some patients with therapy, re-

lapsing and remitting courses are common, and patients often have progressive functional impairment from irreversible airflow obstruction.

Given the importance of supportive data to make a diagnosis of GVHD-associated obliterative bronchiolitis, it is critical to have accurate and reproducible physiologic data. In this case the discrepancies between 2 methods of lung-volume measurement led to substantial clinical disconnect and consideration of more invasive diagnostic interventions. The 2 most common methods for measuring lung volumes are gas dilution techniques (helium dilution or nitrogen washout) and body plethysmography.^{6,7} Helium dilution or nitrogen washout techniques underestimate FRC (and thus residual volume and total lung capacity) in patients with dynamic gas trapping and ventilatory gas distribution abnormalities. Areas of the lung with long time constants (the time constant is the product of lung compliance and airways resistance) are more poorly ventilated and thus will take a longer time to wash out the inhaled nitrogen than will the better-ventilated regions. The final concentration of the washout nitrogen may be substantially affected by the duration of the washout period and by the heterogeneity of ventilation. If the washout technique is terminated too early, poorly ventilated areas with long time constants will incompletely empty. As a result, the lung volume measurement will be lower, leading to an underestimation of FRC.

Body plethysmography is the accepted standard for lung volume measurements.^{6,8} However, body plethysmography has the potential to overestimate lung volumes when a large amount of compressible abdominal gas is present or there is substantial heterogeneous gas distribution, resulting in the underestimation of alveolar pressure differences.^{9–15} Nonetheless, the potential limitations of body plethysmography are considered less functionally important than those of nitrogen washout and, if present, will still result in the correct characterization of the underlying physiology.

In the patient presented above, based on the CT finding of mosaic attenuation with hyperinflation, we believe that lung volume was underestimated by the nitrogen washout technique, rather than substantially overestimated by body plethysmography.

In summary, our patient had GVHD-associated obliterative bronchiolitis following allogeneic bone marrow transplantation. The nitrogen washout technique substantially underestimated lung volume because of dynamic gas trapping. Care providers must be knowledgeable of the pulmonary complications of allogeneic bone marrow transplantation as well as the scientific principles and physiologic limitations guiding the various methods to measure lung volumes. Clinicians should also maintain a critical eye for potential errors, such as in the case described. Failure to do so may lead to incorrect or delayed diagnosis, additional unnecessary testing, or inappropriate or delayed therapeutic intervention.

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